

studies, collaborating with investigators from Cornell University and Case Western Reserve University.

In these experiments, Yang gave a group of mice only tea to drink, and he also gave them, as well as a control group, chemicals known to produce different cancers. Among the animal "tea" models he has developed are those for lung, esophageal, and forestomach. He found that mice fed tea developed fewer tumors than the control group and that their tumors were smaller. His latest study on tea's protective effect on skin cancer was published in July in *Cancer Research*.

Although there are numerous theories as to why tea may offer protection, most scientists think it is due to polyphenols, such as flavanols, which make up 30% of the dry weight of the tea. These chemicals not only possess strong antioxidant activities, but they can also inhibit nitrosation reactions, modulate carcinogen-metabolizing enzymes, trap carcinogens, and inhibit cell proliferation.

Yang said that he can demonstrate that tea scavenges free radicals produced by oxidation reactions in the body, "but whether that is at the heart of the anticancer action remains to be studied." He co-authored a major review discussing the contradictions in the study of tea and cancer, published last July in the *Journal of the National Cancer Institute*. "It will be very difficult to pinpoint how it works in humans," said Yang. "The protective effects may be small in humans; it may just get lost in a host of other mechanisms."

To help point to an answer, Yang is working with the Beijing Cancer Institute to design an intervention study in China. It will follow thousands of people who will take capsules of tea powder daily to see if the rate of stomach cancer that develops in this population is reduced.

Bernard Goldstein, director of the Environmental and Occupational Health Sciences Center in New Jersey, welcomed a renewed interest in tea, which he first studied 20 years ago. "The studies in animals are very encouraging," he said, "and there is enough information about the effect of tea in humans that it makes one want to do careful and thorough epidemiological evaluation."

A Breath of Fresh Air

Flight attendants and passengers may soon be breathing easier if a bill called the Safe Cabin Air Quality Act is passed. The bill (HR 2985), introduced in August 1993 by Congressman Jerrold Nadler (D-New York) in response to health complaints associated with reduced fresh air, would increase the amount of fresh air pumped

into airline cabins.

In response to concerns over anticipated increases in the cost of fuel in the late 1970s, airlines studied ways to conserve fuel. It was discovered that energy could be saved by reducing the amounts of fresh air pumped into airplane cabins. For example, a McDonnell-Douglas study in 1980 found that if the amount of fresh air was cut by 50% on a DC-10 trip of 1,050 miles, the airline could save 0.8%, or 42 gallons, of fuel. Since the 1980s, the volume of fresh air circulated in most airline cabins has been cut by about half from 100% fresh air pumped in every 3 minutes to half fresh and half recirculated air every 6–7 minutes. This drastic reduction has been blamed for headaches, nausea, dizziness, and other health problems experienced by flight attendants and passengers. Chris Witkowski, director of air safety and health for the Association of Flight Attendants, says that there are some asthmatics who will not fly now because of difficulties with breathing. "It's going to be a growing health problem," he said.

In 1993, using the current domestic cost of \$0.59 per gallon for jet fuel, Witkowski divided the average number of passengers on a 1,050 mile trip on a DC-10 into the price per gallon, multiplied by 42, the number of estimated gallons of fuel saved, and found that the airlines were saving \$0.13 per passenger. "The average passenger would pay that much to double the amount of fresh air they get on a flight," Witkowski said.

At such a small percentage of savings, many wonder why airlines would reduce the amounts of fresh air. Because the Federal Aviation Administration has failed to impose guidelines on cabin air quality standards, airlines have had no disincentive to save some money. "There is a tendency for airlines to want to reduce fresh air as much as possible to squeeze every nickel out of the cost of fuel," Witkowski said.

Browner v. Bush

In July, EPA Administrator Carol M. Browner proposed to overturn a decision by the Bush administration which eased regulations on industries under the 1990 Clean Air Act in the name of industrial growth. Browner's proposal would grant environmentalists a rule that would require a period of public comment on potential increases in emissions when industries attempt to gain permits to expand their operations.

In 1992, Bush handed down a decision that allowed industries to expand their operations even if the expansion would cause higher levels of emissions than allowed by the permits they had obtained. Environmentalists protested, fighting for a provision that would allow public input on changes in emissions before expansion could take place, but the White House Competitiveness Council argued that such a provision would slow the permitting process and restrict attempts to bring the country out of recession.

The proposed rule is to take effect after a 90-day comment period. Browner's decision stems from negotiations with environmentalists mobilized by the Natural Resources Defense Council, who sued the EPA following Bush's decision. The environmentalists and EPA officials have agreed to reach an out-of-court compromise.

The FAA does regulate the maximum amount of carbon dioxide in airline cabins at a standard of 30,000 parts per million. But Witkowski called the figure "absurd," and said it is "virtually meaningless at that level." The level that the American Society of Heating, Refrigeration, and Air Conditioning Engineers associates with satisfaction or comfort is 1,000 ppm. And the Occupational Safety and Health Association is considering setting a standard of 800 ppm in workplaces.

Several studies have been done that link recirculated air to transmission of viruses and bacteria. Studies by the U.S. Centers for Disease Control have not been able to rule out the possibility that tuberculosis could be transmitted among passengers. Last year a report said that a flight attendant with active tuberculosis infected 13 fellow workers before being diagnosed and treated. Airlines argue that their filtration systems mitigate potential exposures, but a recent study conducted by researchers at the Harvard University School of Public Health questioned the adequacy and effectiveness of strategies used by airlines. The researchers recommended further studies be done before conclusions are made.

Despite these findings, the Air Transport Association recently concluded that reducing fresh air in cabins is safe for passengers and airline crews, outraging airline flight attendants who want the levels of fresh air raised. "We feel it is critical for the federal government to set some standards for cabin air quality. Until this is done, the quality of air is going to get worse," Witkowski said.

Flight attendants are also urging the government to take into account the range of people that travel. Not all airplane passengers are able-bodied workers; among those who fly are asthmatics, the elderly, people with allergies, and people whose immune systems have been impaired by

chemotherapy or HIV. Therefore, flight attendants and others say that airplane cabin air should be held to higher standards than workplaces.

Pressure from passengers may be a major contributing factor in encouraging airlines to increase fresh air. In the August issue of *Consumer Reports*, airlines were ranked according to levels of carbon dioxide in airplane cabins and criticized for the low amounts of fresh air. *Consumer Reports* recommended that passengers choose airlines according to the amounts of fresh air they circulate. They also recommended that the FAA set a comfort standard of 1,000 ppm.

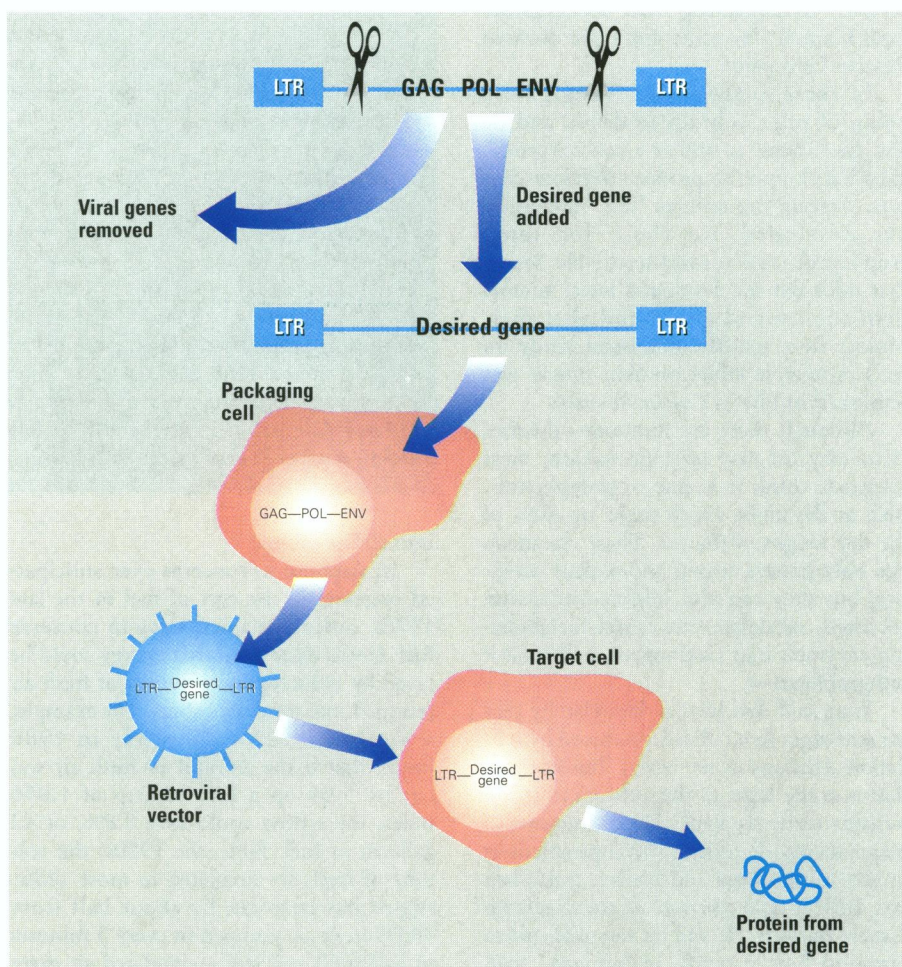
Double-Edged Sword?

Although individuals with genetic disorders and diseases such as cancer, AIDS, diabetes, or Alzheimer's may view the potential of gene therapy as just the weapon they're looking for, other people perceive the "slicing and dicing" of genetic material as a potential double-edged sword. Scientists are attempting to estimate the real risks associated with gene therapy.

Most current gene therapies use retroviral vectors to transfer a therapeutic gene into the cells of a patient who lacks a normally functioning copy of the gene. Retroviral vectors are made by deleting portions of a retroviral genome and replacing the deleted viral genes with the therapeutic gene. The resulting vector integrates a DNA copy of its genome, containing the therapeutic gene, into the genome of a host cell, but because of the missing viral genes the vector cannot be replicated like a normal retrovirus.

Typically, bone marrow cells are removed and exposed to the vector in culture. The cells containing the therapeutic gene are then infused back into the patient. The fear is that the vector may integrate its DNA copy near a gene involved in regulation of growth or development of the cell and interfere with the normal regulatory processes, causing the cell to become cancerous. Although, says toxicologist Richard Irwin of NIEHS, "there is absolutely a finite probability that it will occur," the risk of insertional mutagenesis is believed to be very low. The difficulty comes in trying to determine exactly what "very low" means in terms of absolute risk to humans from gene therapy.

Scientists are concerned about other potential side effects of the process of gene therapy. First, it is not currently possible to target a vector carrying a therapeutic gene to a specific cell population. Expression of the gene in nontargeted cells may interfere



Cut and paste. Retroviral vectors are made by transferring a modified retrovirus into a packaging cell which produces the desired protein in a target cell.

with regulation of cell processes or metabolic pathways. Second, the transduced cells may contain a selective growth advantage, enabling their progeny to predominate in the host. When such cells are introduced into a patient during gene therapy, they represent a population carrying a "first hit" insertional event that may put the patient at increased risk for additional mutational events leading potentially to tumor formation. Third, retroviral vector preparations may be contaminated by virions containing packaging cell RNA. In theory, this RNA could be reverse-transcribed, integrate in the genome of the recipient cells, and express a product that could disrupt normal cell functioning.

The risk posed by insertional mutagenesis is a particular concern for extending gene therapy to the treatment of conditions such as diabetes or hemophilia where substantial numbers of people would be candidates for the therapy and might be treated early in their lives. A population of cells carrying a first hit insertional event would put such people at an increased risk throughout the remainder of their lives.

As gene therapies are expanded for the

treatment of more diseases, the sheer numbers of people involved makes it more likely that even a relatively infrequent event may result in an unacceptably high risk. Irwin and his colleagues at the NIEHS are developing studies to attempt to evaluate the extent of this risk. In these studies, researchers will expose mice and rats to retroviral vectors in a number of ways. These vectors contain marker genes which allow the researchers to determine the most effective method of integration of the vector into the new cell genome. The animals are allowed to live out their life spans, and researchers then examine them to see if they developed tumors, and if so, if the tumors contained DNA from the retroviral vector. The information from these studies will be used to estimate gene therapy's risk and may help regulators evaluate the safety of cutting edge technology.